Review

Jeremy Winkelman*, Diep Nguyen, Eric vanSonnenberg, Alison Kirk and Steven Lieberman

Artificial Intelligence (AI) in pediatric endocrinology

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Abstract: Artificial Intelligence (AI) is integrating itself throughout the medical community. AI's ability to analyze complex patterns and interpret large amounts of data will have considerable impact on all areas of medicine, including pediatric endocrinology. In this paper, we review and update the current studies of AI in pediatric endocrinology. Specific topics that are addressed include: diabetes management, bone growth, metabolism, obesity, and puberty. Becoming knowledgeable and comfortable with AI will assist pediatric endocrinologists, the goal of the paper.

Keywords: Artificial Intelligence (AI); pediatric endocrinology; review

Introduction

Medical knowledge is expanding rapidly, estimated to double every 73 days [1, 2]. Today's physicians are becoming increasingly reliant on digital tools to better assist them in medical decisions during this onslaught of information [3]. Artificial Intelligence (AI) is one of the most powerful assets for information processing that currently exists. AI is well-suited to analyze vast amounts of information efficiently, and has the potential to positively influence many medical specialties due to its complex pattern analysis abilities. The applications of AI already have been applied, and are continuing, to revolutionize various medical fields, such as genetics [4], oncology [5], imaging [6], and pharmacokinetics [7]. This paper serves to summarize the main advancements of AI in pediatric endocrinology. Furthermore, we provide predictions on what future challenges AI might address in the field.

Pediatric endocrinology, as a subspecialty of pediatrics, encompasses a wide range of endocrine abnormalities. The diseases that pediatric endocrinologists frequently encounter consist of: growth problems; early or delayed puberty; thyroid, pituitary, adrenal gland, pancreatic, ovarian, and testicular dysfunction; diabetes; hypoglycemia; obesity; and vitamin D problems [8]. AI can enhance the ability to detect pediatric endocrinologic disease early and accurately [9]. This can be extremely valuable for timely interventions and improved outcomes in children. AI also can be used to effectively automate preventive screening tools to detect diseases. Becoming knowledgeable and comfortable with AI can assist pediatric endocrinologists, the true goal of this paper.

We will now address these individual areas in-depth with respect to AI.

Diabetes

Type 1 diabetes is characterized by autoimmune destruction of insulin-producing β cells in the pancreas by CD4+ and CD8+ T cells and macrophages that infiltrate the islets [10]. A large portion of the patients a pediatric endocrinologist sees are those with type 1 diabetes. From 2001 to 2017, the prevalence of type 1 diabetes in children in the United States increased from 1.48 per 1,000 children to 2.15 per 1,000, and the prevalence of type 2 diabetes in children in the US also increased from 0.34 per 1,000 children to 0.67 per 1,000 [11]. Managing the insulin regimen is a major aspect of these patients' health. In a study using an AI decision support system, recommended insulin dose adjustments were

***Corresponding author: Jeremy Winkelman**, MS4, University of Arizona College of Medicine Phoenix, HSEB Building C523, 475 N 5th St, Phoenix, AZ 85004, USA, Phone: 602 827 2611, E-mail: jwinkelman@arizona.edu
Diep Nguyen, University of Arizona College of Medicine Phoenix, Phoenix, USA
Eric vanSonnenberg, University of Arizona College of Medicine Phoenix, Phoenix, USA; From the Departments of Radiology, University of Arizona College of Medicine Phoenix, Phoenix, USA; and Student Affairs, University of Arizona College of Medicine Phoenix, Phoenix, USA
Alison Kirk, University of Arizona College of Medicine Phoenix, Phoenix, USA; Student Affairs, University of Arizona College of Medicine Phoenix, Phoenix, USA; and Pediatrics, University of Arizona College of Medicine Phoenix, Phoenix, USA
Steven Lieberman, University of Arizona College of Medicine Phoenix, Phoenix, USA; and Internal Medicine (Division of Endocrinology), University of Arizona College of Medicine Phoenix, Phoenix, USA

similar between expert pediatric endocrinologists and AI [12]. This highlights the potential incorporation of AI as a decision support tool to assist physicians with insulin dose adjustments and titrations.

Diabetic retinopathy is a well-known complication of diabetes and a major cause of vision loss worldwide. The American Diabetes Association recommends screening for diabetic retinopathy in children 11 years or older with a dilated ophthalmologic examination or retinal photography [13]; unfortunately this is not always feasible or followed. Detecting early diabetic retinopathy is an area in which AI is making strides. Utilizing an AI system for diabetic eye exams may become a reality to aid management in diabetic children. In one study involving children with diabetes at a multidisciplinary pediatric diabetes center, an AI system was used to detect the presence of diabetic retinopathy with a sensitivity of 85.7 % and a specificity of 79.3 %. The use of an AI system also was found to improve adherence to screening guidelines in this setting [14]. Another adult AI system is performing at even higher levels compared to the childhood AI system; AI predicted diabetic retinopathy in a primary care population with a sensitivity of 87.2 % and a specificity of 90.7 % [15]. Although this evidence was used in adult populations, it could potentially be applicable to children in the future.

Machine learning systems have been developed to predict the diagnosis of diabetes in adults through electronic health groups. One group used data by a machine learning algorithm to determine who had type 2 diabetes, based off data points listed in the electronic health record out of a population of over 23,000 people. Some of the data points included patient demographics, patient communicated symptoms, laboratory results, medications, and inpatient and outpatient diagnosis records. This system had a mean area under the curve (AUC) of 0.98 [16], a testament to the system's accuracy. Predictive models show the feasibility of identifying adults who have a high probability to develop undiagnosed diabetes. Studies such as these are promising, and eventually may be applied to predict children who will develop diabetes.

Another serious complication of diabetes is chronic kidney disease, defined as elevated urinary albumin excretion or impaired renal function [17], which approximately one-third of patients with type 1 diabetes will develop [18]. One study in adults used AI to predict diabetic kidney disease progression with 71 % accuracy [19], which is another promising example of a potential application for children in pediatric endocrinology in the future. To date, there are no studies that have looked at the use of Al for prediction of diabetic-associated kidney disease in children with diabetes, although AI's utility may be anticipated.

There are currently 3 FDA approved AI-based devices related to diabetes management [20]. Two are designed to manage blood glucose monitoring with continuous glucose monitoring predictive alerts [21]. The third interprets ophthalmologic results to detect early diabetic retinopathy [22].

Short stature and bone growth

Monitoring that recognizes abnormalities in growth can indicate serious diseases accurately [23]. Bone age is one of many parameters pediatricians use to determine potential causes of growth abnormality, although assessing bone maturation does not necessarily translate into improved diagnostic accuracy. Deep learning neural networks have been shown to estimate pediatric skeletal maturity from ages 1.5–18.2 years with similar accuracy to expert radiologists [24]. Additionally, screening of growth disorders using algorithms integrated into a Finland EHR system resulted in higher and earlier rates of detection and referrals to specialists, compared to standardized growth monitoring. Some of these diagnoses include celiac disease and Turner's syndrome [25].

A system called the fully automated deep learning system for bone age assessment was created in 2017 by a group of researchers from Massachusetts General Hospital. This convoluted neural network was able to assess bone age using female radiographs within 1 year with 90.39 % accuracy; male radiographs could be predicted accurately at 94.18 % to within 1 year of actual bone age [26]. The Radiology Society of North America in 2017 created a competition to best estimate bone age assessment using machine learning. One AI company achieved accuracy of hand bone age within an average of 4.3 months [27].

Another fully automated AI system studied pediatric Chinese patients with abnormal growth and development to predict bone age. The accuracy of this automated AI system within 1 year was 84.60 %, compared to the reference standard, with the highest percentage of 89.45 % in the 12- to 18-year group [28].

An area in which AI and machine learning shine, is in interpreting medical images and helping physicians make diagnoses. AI can assist in analyzing heterogeneous variables such as facial structure. One machine learning algorithm showed better sensitivity, specificity, positive predictive value, and negative predictive value compared to physicians for diagnosing acromegaly by using early detection of facial changes imaging [29].

Thyroid nodules

The incidence of thyroid cancer in the US adolescence is increasing, with an annual percentage change of 3.44 for males, and 3.81 for females [30]. Therefore, a reliable method to differentiate benign from cancerous nodules accurately would be valuable clinically. AI is being used to help establish the diagnosis and management of pediatric thyroid diseases. One deep learning algorithm was used to differentiate benign and malignant thyroid nodules on ultrasound in children and young adults. The algorithm had a sensitivity of 87.5 %, which was higher compared to the average sensitivity of 58.3 % from radiologists, although lower for specificity (36.1 % compared to average of 79.9 %) [31]. It is suggested that this improvement in diagnostic performance could help reduce unnecessary fine needle biopsies for thyroid nodules [32].

Metabolism and obesity

Another focus of pediatric endocrinology is childhood obesity and metabolism. According to the CDC, “For children and adolescents aged 2–19 years in 2017–2020, the prevalence of obesity was 19.7 % and affected about 14.7 million children and adolescents.” [33].

Using AI to analyze clinical signs and symptoms to help predict childhood obesity can lead to earlier interventions and lifestyle modifications. Current non-AI tools to estimate future obesity are imprecise, and utilize variables such as family history, eating habits, exercise levels, and overall activity levels. AI has numerous opportunities to improve patient outcomes in this area. Using machine learning techniques, one group was able to predict childhood obesity in children less than 2 years old with an accuracy of 85 % and a sensitivity of 89 %. They analyzed nine years of clinical information from 7,519 patients from four hospitals. The machine learning algorithm included biometrics, including child weight, height, race, and vital signs, as well as other variables including insurance status and use of a walker. They determined the most important factor for predicting obesity was overweight before 24 months [34].

Resting energy expenditure represents the expended energy while patients lay quietly with little movement. It is the largest component of daily caloric expenditure, and the gold standard of measuring it, an indirect calorimetry, often is not available in the clinical setting. One group developed a neural network, using weight, height, and sex as clinical inputs, that was able to measure the resting energy expenditure in obese patients to a better degree than established equations. This is clinically significant because an accurate assessment of energy needs is necessary to determine what appropriate dietary changes can be recommended; this can guide proper nutritional prescription in critically ill children [35, 36]. Another artificial neural network estimated resting energy expenditure in pediatric ICU patients using data input. The data includes nutritional status, vital signs, biochemical values, and $VC0_{2,}$ and reached an accuracy of 89.6 %, greater than commonly used predictive equations [36].

Metabolic syndrome is a group of various disorders that ultimately can lead to heart disease, stroke, or type 2 diabetes. Clinical data also have been able to help predict Metabolic syndrome using an artificial neural network. It is difficult to estimate the prevalence of metabolic syndrome in children because many different criteria have been used in its various definitions. Different publications have described prevalence numbers ranging from 0.2 to 38.9 %. The incidence of metabolic syndrome is a range, depending on criteria used, although it is certain that the overall incidence has increased over time [37]. One machine learning algorithm used data input that included demographic information, home address, vital signs, medications, maternal vital signs, and maternal laboratory results, before, during, and post-pregnancy. It was able to predict obesity at year 5 from children less than 2 years old, with an AUC of 81.7 % for girls and 76.1 % for boys [38]. Machine learning algorithms also have been deployed to predict the success of therapies for decreasing childhood obesity and related outcomes. One study aimed to predict the success of a 6-month weight loss therapy for a cohort of 20 adolescents from Switzerland. The machine learning algorithm used factors including weight, age, BMI, height, and heartrate during a run test; it was able to predict success of therapy with an 85 % accuracy, performing better than domain expert predictions [39].

Puberty

Central precocious puberty, or the early activation of the hypothalamic-pituitary-gonadal axis, is defined by, “the early development of secondary sex characteristics, acceleration of linear growth, advanced bone age, and a pubertal response to gonadotropin-releasing hormone (GnRH) test” [40]. Pediatric endocrinologists diagnose and treat patients with pediatric precocious puberty and other areas of puberty dysfunction.

A machine-learning based diagnostic model was used to determine if female children with an already established diagnosis of precocious puberty had a central cause. Of the 614 patients with this already established diagnosis, 85 % had *central* precocious puberty. The machine learning tool used inputs including age, BMI, secondary sex characteristics, bone age x-ray results, and laboratory tests. This machine learning model was able to predict central precocious puberty with a positive predictive value of 0.987, area under the curve of 0.972, and a specificity of 0.893 [41]. The benefits of this technology would be to reduce the number of blood samplings, as well as to provide results more efficiently than the standard GnRH stimulation test. A different machine learning diagnostic model, using laboratory data on 1,757 girls, was able to predict central precocious puberty with sensitivity ranging from 77.91 to 77.94 %, and specificity ranging from 84.32 to 87.66 %. They determined that serum luteinizing hormone, follicle-stimulating hormone, and insulin-like growth factor levels were the most important predictive input factors [42].

Machine learning algorithms have been applied to the detection of subtle dysmorphic facial features. Congenital adrenal hyperplasia (CAH) is a common pediatric primary adrenal insufficiency condition that leads to a hormonal excess, such as from testosterone and estrogen. Although there are many distinct characteristics of CAH, differences in morphologic facial features are not a classic aspect of it. A cross-sectional study in Southern California used a machine learning algorithm to determine whether subtle dysmorphic facial changes would be enough to predict CAH. This study was able to achieve a mean AUC of 92 % for predicting CAH, from just facial images that had distinct, subtle, and morphologic changes [43].

Early timing of menarche has been linked to adverse health outcomes, including obesity, asthma, and type 2 diabetes [44]. Certain endocrine disrupting chemicals can impact when female patients begin menarche. One study used machine learning to determine if exposure to certain combinations of endocrine disrupting chemicals had an impact when menarche began; it was able to determine several interpretable combination of biomarkers. For example, lower levels of mono-(2-ethyl-5-hexyl) phthalate (MEHP), a metabolite of Di-2-ethylhexyl phthalate (DEHP) that is a type of phthalate that often is used in plastics to increase flexibility [45], corresponded to earlier onset of menarche [46]. This information is an example of how machine learning can be used to screen efficiently for new chemicals with appreciable effects on disruptions to human endocrinologic pathways.

Limitations of AI

Although AI offers much potential to enhance pediatric endocrinology, it has limitations. Machine learning algorithms are most effectively trained on large, standardized data-sets; thus, since psychological status and changes in social factors are not standardized data-sets, they are not amenable to machine learning algorithms.

Breach of private health data used in electronic health records that could be used to train AI algorithms would be catastrophic [47]. Currently, there is no focus on training or educating endocrinologists in the use of these technologies for diagnosis or research [9].

Most importantly, AI does simulate the doctor–patient relationship. Patients want and deserve human connection when interacting within the health care system, and that is something that physicians do, but AI cannot.

Conclusions

AI's ability to analyze complex patterns and interpret large amounts of data will have considerable impact on all areas of medicine, including pediatric endocrinology. While the influence of AI surely will expand in the future, it is already having an impact. This paper has highlighted advances AI has made in diabetes management, bone growth, metabolism, obesity, and puberty. The future is bright for AI to be a valuable adjunct for pediatric endocrinologists.

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